POTENTIAL DRUG LEADS FROM MARINE SOURCES FOR DEPRESSION: AN *in silico* APPROACH

A

RESEARCH SYNOPSIS

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Introduction

"Depression"- the word is very familiar now a days. Almost half of the world faces depression in his or her life during some stage. This may extent to certain extent that a person becomes mentally ill and feels nervous all the time. Lots of research has been taken place to findout some potential lead compounds that can show interactions with these targets.

Worries, upsetting or stressful life events, different drugs even use of social networking can beconsideredascauseofdepression.ThereportonGlobalBurdenofDiseaseestimatesthepoint prevalence of unipolar depressive episodes to be 1.9% for men and 3.2% for women, and the one-year prevalence has been estimated to be 5.8% for men and 9.5% for women. It is estimated that if current trends continue to increase, the burden of depression will increase to 5.7% of the total burden of disease. (Lopez AD, et at.,2006).

Studies on the elderly population, either in the community, inpatient, outpatient and old age homes have shown that depression is the commonest mental illness in elderly subjects (Nandi PS et al., 1997).

There are wide variety of drugs available but most of them show some or the other side effect. There is need to find alternative to this type of drugs that posses anti-depressant activity withleastornosideeffects.Andthisiscanbepossibleifweexplorenaturalcompounds.There is research being carried on for phytochemical extracts of plants for anti-psychotic activity. Similarly, wide variety of marine compounds is also found to show activity against this.

The marine environment has been explored in the search for new bioactive compounds. Marine invertebrates have proven to be an outstanding source of active molecules, one of the most promising being indole alkaloids. E Fattorusso,O Taglialatela-Scafatiinformed about different alkaloids in their book "Modern alkaloids: structure, isolation, synthesis, andbiology". Alkaloids from different natural sources, isolation, structures, activity and their synthesis were enlisted.

Compounds like neratriptan, almotriptan, eletriptan, favotriptan, etc anti-depressant activity. Serotonin is one of the neurotransmitters present in the central and peripheral nervous system which plays an important role in normal brain function and regulates sleep, mood,

appetite, sexual function, memory, anxiety and many others (Nichols DE et al., 2008). The structural similarity of indole alkaloids to endogenous amines and neurotransmitters has led researchers to postulate the possible neurological activity of these molecules.

It is very necessary to understand the need of natural substances for curing such psychotic disorders as the synthetic drugs available are having lots of side effects. Hence, most of the attention is to identify natural compounds that beneficially replace these drugs with adverse side effects. There are different research being carried on compounds obtained from marine sources that show bioactivity against therapeutic targets. This research aims to identify compounds obtained from marine sources that can be potent anti- depressants by using *in silico approach* so that we ought towards natural sources as anti-depressants rather than using medicines showing adverse side-effects.

Literature Review

According to S. Ekins et al. (2007), *insilico*methods are primarily used alongside the generation of*in vitro*data both to create the model and to test it. Increasingly over the last decade however we have seen that computational (*in silico*) methods have been developed and applied to pharmacology hypothesis development and testing.*In silico*pharmacologyis a rapidly growing area that globally covers the development of techniques for using software to capture, analyse and integrate biological and medical data from many diverse sources.

Kitchen, D. B. et al. (2004) described molecular docking as it accurately predict thestructureofligandandreceptorbindingposesandcorrectlyestimatethebindingstrength.Although docking scores are highly susceptible to preparation conditions of active sites and ligands, the comparison of them under exactly determined conditions constitutes a great indicative of the relative activity of the tested molecules as inhibitors of the target enzyme.

Margulis, L., & Schwartz, K. V. (1998) stated that marine environment is a natural habitat for diverse living organisms having different physiology and capacity to adapt their environment. Out of over 33 animal phyla known today, a total of 32 phyla are embodied in the marine environment out of which 15 varieties are exclusively present in the marine environment (Margulis, L., & Schwartz, K. V., 1998).

Thakur NL in his paper “Marine natural products in drug discovery” (2005) gave information about marine organisms found in India. They stated that approximately a half of the total biodiversity, offers vast source to discover useful therapeutics. In recent years, a significant number of novel metabolites with potent pharmacological properties have been discovered from the marine organisms. India has over 8000 km of coastline with clusters of marine habitats. The potential of Indian marine habitat has remained largely unexplored for their potential of new drugs and biotechnological programs. Only some of the selected institutes are presently working for exploration of life saving drugs from marine sources.

A review article by S. Munir et al. investigated the bioactive compounds from plants and marine sources that contain the indole moiety, which can serve as potent antidepressants. The prospectsofnaturallyoccurringaswellassyntheticindolealkaloidsfortheamelioration ofanxiety

and depression-related disorders, structure-activity relationship, and their therapeutic prospectshave been discussed.

The research article by B. Yan et al. suggested acupuncture has a promising application prospect due to its unique advantages for the treatment of chronic pain with depression comorbidity, which can be used in patients suffering from some certain chronic pain with depression comorbidity with poorer response to the conventional medication or suffering from serious side effects.

According to studies carried out by Anna j Kochanwska et al. (2008), brominated indole alkaloids are a common class of metabolites reported from sponges of the order Verongida. Three species from this order showed similarities in secondary metabolites. Two of the three species were identified containing brominated compounds as well as sesquiterpene quinines and hydroquinones. This study provides evidence that marine natural products with the diversity of brominated marine alkaloids will provide potential leads for anti-depressant and anxiolytic drugs.

Objectives

1. To identify targets related to depression.
2. To identify the compounds obtained from marine sources for potential anti-depressant activity.
3. Dock the potential ligands with therapeutic target to check their binding affinity.
4. To evaluate the scores generated in docking.

Methodology

This research will be focusing on comparison of binding affinities or scores of ligand compounds obtained from marine sources. Main pillars of this research will be to predict the activity of these compounds with the target and to identify the potential of.

For carrying out the target-ligand interaction, one must be totally aware of the properties of ligand and its relevant target. After selecting compounds after literature survey, their information will be obtained from chemical databases which give information about 2D and 3D structure of lead compounds.

There are different sources from which 3D structure of target can be obtained like PDB, MMDB, SWISS-PROT repositories, etc. These structures need to be downloaded in proper format so they fulfil the criteria of input format in different docking software. Dominantly PDB will be used for accessing the structures of targets. Ligand structures will be taken from chemical databases like PubChem or DrugBank.

Selection of software used for docking as well as scoring is also very important. Hence, it is very initialsteptoevaluatedifferentsoftwareonthebasisofalgorithmstheyuseandresulttheyprovide. Here AutoDock will be used for docking and to obtain different conformations of ligands with target.

Are the compounds really potent for curing different diseases? Can it be replaced with costly and non-native drugs? Does it act as potent as different allopathic drugs? These all questions can be easily answered after such study.

Importance of study

It is necessary to validate the action of bioactive compounds obtained from different natural sources. It will be helpful for countries which are having large availability of marine animals or plants. Or countries which are economically backward and cannot afford costly medicines. They can make use of such findings. It will give new hope to conserve this biodiversity which is under threat of extinction due to our ignorance. Further research can be carried out to check if any other compound in combination to potent compounds can enhance their activity to interact with target.

Proposed work plan

YEAR	TARGETS TO BE ACHIEVED
1st	Going through the literatures available related to the research topic. Identifying different chemical compounds from marine sources.
2nd	Obtaining structures of ligands and their target. Docking them and generating scores. Attending workshops/trainings/conferences.
3rd	Analyzing the result generated. Publication of research articles. Thesis writing.

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